

Gut

Leading article

Role of cytokines and their inhibitors in acute pancreatitis

Acute pancreatitis is a disease with considerable lethality for which there is no specific therapy beyond supportive treatment. Epidemiological data on the disease are sparse, but the incidence in Western countries is in the region of 10–20 per 10⁵ population.^{1–3} There are probably up to 10 000 cases of acute pancreatitis annually in Britain and as the mortality is approximately 8–12%, overall mortality may approach 1000. In Finland the incidence has increased by 50% between 1970 and 1989.⁴ Hospital discharges with the final diagnosis of pancreatitis correlate with alcohol consumption in men and with gallstone disease in women.

The early pathophysiology of the disease is not well understood. After the initial acinar cell injury, inflammatory cells migrate into the interstitium by adhering to endothelium and escaping from the microcirculation. The mechanisms by which inflammatory cells adhere to endothelial cells are determined by a variety of mediators or cytokines released at sites of tissue damage. Cytokines hold the key to both the local and the systemic inflammatory response in acute pancreatitis. New therapeutic approaches aim to modulate these pathways.^{5 6}

Acute pancreatitis

Whatever the initiating event, the disease can be regarded as progressing in three phases—that is, a local inflammatory response, a systemic inflammatory response that can result in an organ or multiple organ failure, and finally the intervention of infection by translocation of bacteria from the gut.

Initiation

Recent investigations have established that pancreatitis from whatever cause, disrupts the normal stimulus-secretion coupling within the acinar cell.⁷ This disruption within the acinar cell leads to an event termed 'co-localisation' in which the digestive and lysosomal enzymes merge resulting in premature activation of proteases.⁸ As a result there is a preference for basolateral rather than apical protease secretion and hence release of these enzymes into the pancreatic interstitium.⁹ Many treatments have been directed to inhibit this 'autodigestive' process. However, protease inhibition has been singularly ineffective in treatment of the disease: trasyolol, fresh frozen plasma, and peritoneal lavage have been abandoned. The newer low molecular weight antiprotease inhibitor gabexate mesilate, and the somatostatin analogue, octreotide have shown some promise in reducing complications but have no effect on mortality.^{10 11}

Disruption of the acinar cell propagates a macrophage derived cytokine response. Much of the complications and lethality of acute pancreatitis result from the amplifying effects of the disruption of the microcirculation. In an absence of an understanding of the intra-acinar cell initiating events (and indeed many patients will arrive in hospital long after these initiating events triggered the damage) a logical strategy of damage control is anti-cytokine therapy, to modulate the inflammatory response, downregulating the systemic effects and organ failure.¹²

Because of the typically rapid onset of acute pancreatitis and the relative inaccessibility of human pancreatic tissue it is necessary to study the pathophysiology of the disease in experimental models. There are imperfections in this approach and successful treatments in experimental models are frequently of no benefit in the clinical disease. Nevertheless, in recent years study of a variety of models has enabled a better understanding of the time course of pathophysiological events.^{13 14}

The inflammatory response

The key to an understanding of the pathophysiology of acute pancreatitis lies in discovering why a proportion of patients progress from a limited local inflammation to a potentially dangerous systemic inflammatory response. The probable cause is high levels of circulating pro-inflammatory cytokines, which induce activated white cells to escape into the tissue parenchyma of lungs, kidneys, liver, haemopoietic and vascular system. Cytokine release from tissue macrophages are thought to be the trigger for the cytokine cascade. This event leads to the migration of blood monocytes and neutrophils to the site of injury and these cells are then capable of secreting a large variety of damaging inflammatory mediators. The degree to which these mediators escape into the circulation contributes to the induction of the systemic inflammatory response syndrome (SIRS), acute phase response, and multiple organ failure.^{15 16} Organ dysfunction occurs in one in four patients with acute pancreatitis and 60% of patients who die in the first week of the disease die from pulmonary damage resulting from adult respiratory distress syndrome.¹⁷

Infection

Deaths after the first week of the disease are likely to be related to infection.¹⁸ Necrotic pancreatic tissue becomes contaminated with Gram negative bacteria, particularly

Escherichia coli, indicating an endogenous intestinal origin for these bacteria, which probably reach the pancreas via blood, lymph, bile, duodenal chyme, and the transperitoneal route.^{19 20} Recent evidence suggests that suppression of the local inflammatory response with anti-cytokine therapy significantly reduces bacterial contamination.

Cytokine response

Inflammatory disorders arise when the response is misdirected to normal tissue and persists for longer than it is needed. The evidence for an amplified cytokine response as an important element in the development of complications in acute pancreatitis will be outlined below.

Endotoxin

Is endotoxin the trigger for SIRS in acute pancreatitis? Serum endotoxin assay is difficult. Although endotoxin can be detected in 30–50% of patients with acute pancreatitis and in 90% of non-survivors, it is not prognostic of lethality. Antiendotoxin core antibody can be detected in 85% of patients and in all patients with severe disease, suggesting that at some time during the course of the disease endotoxin exposure occurred. However, in germ free rats unable to mount an endotoxin response, tumour necrosis factor production in acute pancreatitis is the same as in normal rats, suggesting that the cytokine cascade is independent of endotoxin production.^{21–23} As in sepsis, antiendotoxin treatments are unlikely to be an effective therapy in the early stages of the disease. The proximal cytokine cascade is a more logical target.

Tumour necrosis factor

Assay measurements for serum tumour necrosis factor are also problematic, both in terms of sensitivity, ligand binding, and the differentiation of free from bound tumour necrosis factor. Nevertheless serum tumour necrosis factor is detectable in only 10–40% of patients and in 23–45% of non-survivors. In experimental acute pancreatitis tumour necrosis factor exhibits an early peak at two hours after induction of the disease and pre-treatment protocols with anti-tumour necrosis factor antibodies have produced conflicting results in terms of efficacy.^{21 24–27} The ‘fingerprint’ for previous tumour necrosis factor exposure is the measurement of soluble tumour necrosis factor receptors in serum and these can be detected in all patients with mild or severe disease.¹⁴ Present evidence indicates that tumour necrosis factor, which is a predominantly macrophage derived cytokine providing an autocrine and paracrine signal in preference to an endocrine one, is an inappropriate target for anti-cytokine therapy in acute pancreatitis.

Platelet activating factor (PAF)

PAF is a potent biological mediator that exerts its effects in a variety of cells and tissues. PAF primes polymorphonuclear (PMN) white cells and acts as a mediator for the interaction between PMN cells and endothelial cells, facilitating migration of activated white cells into tissue spaces. PAF is a structural component of membrane lipids and is released upon the action of phospholipase A₂, an enzyme known to play a key part in the development of acute pancreatitis.^{27 28} PAF acts at very low concentrations (10^{-12} to 10^{-9} molar) via a cell surface receptor. Regulation of the PAF receptor is one of the mechanisms that can control the action of PAF, which has a role in the mediation

of a number of pathological processes, including asthma, ischaemia reperfusion, allergy, shock, and acute pancreatitis.^{29–32} Because of the therapeutic potential of PAF antagonists over 20 companies have filed patent applications on compounds with PAF antagonist activity.^{33–36} Trials in sepsis, asthma, organ transplantation, and inflammatory bowel disease have been inconclusive. Nevertheless there is compelling evidence that PAF antagonists may be beneficial in the treatment of acute pancreatitis because of the wealth of experimental data available.

PAF is an important mediator in the normal physiological functions of the pancreas gland.^{37–43} PAF stimulates amylase release from isolated rat pancreatic acini and nanomolar injection of PAF into pancreatic arterioles can induce or aggravate acute pancreatitis in rats and rabbits and potentiate lipopolysaccharide damage. Moreover, in immune complex induced, caerulein induced, and taurocholate induced experimental pancreatitis, PAF is released into the pancreas, ascitic fluid, lung, and blood.

Numerous investigators have used PAF antagonists in experimental acute pancreatitis.^{37 40–42 44–49} All reported results are positive, although the agents were given in a pre-treatment regimen. Overall, PAF antagonists ameliorate the severity of experimental acute pancreatitis by reducing serum amylase, oxidative injury, morphological changes, white cell infiltration, vascular permeability in pancreas and lungs, pulmonary damage, blood, and peritoneal PAF exudative concentrations.

Lexipafant, a computer image analysis generated imidazolyl derivative of the Sp² nitrogen compounds, is a powerful PAF receptor antagonist having an affinity for the receptor seven times more avid than PAF itself.³³ In the microvascular ischaemia model of acute pancreatitis, this compound is effective in ameliorating the local pancreatic damage when given after induction of the disease.⁵⁰ Lexipafant has subsequently undergone a successful randomised double blind Phase II clinical trial in human acute pancreatitis.¹³ In this study 83 patients were randomised to receive lexipafant 60 mg intravenously for three days or placebo. Clinical progression was assessed by daily APACHE II scores and organ failure scores and the magnitude of the inflammatory response was assessed by serial measurements of interleukin 8, interleukin 6, E-selectin, PMN elastase, and C reactive protein. Twenty nine patients had severe disease with an APACHE II score of 8 or greater. Lexipafant treatment resulted in a significant reduction in organ failure: seven of 12 patients had resolution of an organ failure while 11 patients remained with an organ failure in the placebo group. In addition there was a significant reduction in the total organ failure scores at the end of medication and lexipafant reduced serum IL 8 ($p < 0.04$) and reduced IL 6 and E selectin. These encouraging results of a downregulation of the SIRS associated with the disease has resulted in the initiation of a Phase III study in patients with severe acute pancreatitis, the results of which are awaited.

Interleukin 1 (IL 1)

IL 1 shares many of the properties of tumour necrosis factor, being regarded as an early inducer of many of the systemic and acute phase responses to injury.⁵¹ IL 1 is difficult to measure in serum and its natural antagonist, interleukin 1 receptor antagonist (IL 1ra) may more accurately reflect the degree to which IL 1 stimulation has occurred.⁵² After major trauma IL 1ra levels precede rises in IL 6 indicating that the IL 1 signal is an early event.⁵³ Commercial availability of IL 1ra antagonists have made sepsis an obvious target for the drug and although Phase II trials were promising Phase III trials have shown no

clinical benefit. Established sepsis, however, probably bears little resemblance to the sterile acute inflammatory response in acute pancreatitis. Promising results in experimental models indicate that recombinant IL 1ra can attenuate the rise in tumour necrosis factor and IL 6 and reduce intrinsic pancreatic damage, lung injury, and mortality.⁵⁴⁻⁵⁶

Interleukin 8 (IL 8)

IL 8 is the PMN activating peptide. Although data are limited IL 8 seems to be the earliest cytokine appearing in serum of patients with acute pancreatitis.¹³ Serum IL 8 correlates with severity of disease: no measurable IL 8 occurs in patients with mild disease, (PMN elastase concentrations <200 mg per ml) and decreases in the serum correlate with clinical improvement.^{57 58} Synthetic IL 8 antagonists should be investigated in experimental disease prior to further clinical evaluation.

Interleukin 10 (IL 10)

IL 10 is a naturally occurring anticytokine that inhibits several functions of macrophages including tumour necrosis factor and IL 1 production and the release of oxygen free radicals. Like IL 1ra and soluble tumour necrosis factor receptors it is a naturally occurring inhibitor. In experimental acute pancreatitis in mice recombinant IL 10 reduces acinar cell necrosis and tumour necrosis factor mRNA expression.⁵⁹ These results reveal a further potential therapeutic strategy.

Interleukin 6 (IL 6)

IL 6 is the principal mediator of the acute phase protein response and may be a natural host defence mechanism. To attenuate this response with therapeutic intervention may have undesirable consequences. IL 6 is an excellent marker of severity of disease with peak values (three to six times baseline) occurring at 48 hours and preceding rises in the acute phase protein C reactive protein. Values correlate with severity and predict outcome.⁶⁰ IL 6 antagonists are currently being designed and produced and are available for testing in the experimental models of acute pancreatitis.

Conclusions

Although a number of treatments are currently available to treat various aspects of pancreatic inflammation, they have failed to make a significant impact on the disease overall. Antioxidant therapy for instance can reduce symptom scores and pain scores in recurrent pancreatitis.⁶¹ Imipenem and cefuroxime antibiotics can reduce the number of septic complications and improve mortality in a subgroup of patients with acute necrotising pancreatitis.^{62 63} What is needed, however, is an effective treatment during the early course of the disease that prevents SIRS and organ failure, and which may also ameliorate necrosis and prevent subsequent infection in the gland. Because of our rapidly increasing knowledge of the mechanisms of the systemic inflammatory response and multiple organ failure in acute pancreatitis, a number of new therapeutic approaches to the disease are in various stages of development.⁶⁴ However, it is vital that clinical trials are not started before adequate laboratory and experimental data are available to fully characterise cytokine networks and identify the dominant mediators in acute pancreatitis. Cytokine inhibitors must aim to downregulate the cascade or ripple effect before the tidal

wave of circulating cytokines overwhelms organ specific microcirculations.⁶⁵

ANDREW KINGSNORTH

*Plymouth Postgraduate Medical School,
Derriford Hospital,
Plymouth,
Devon PL6 8DH*

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A Kingsnorth

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